



NOTES

PERINATAL INFECTIONS

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Infections during pregnancy, birth
 - Teratogenic/other adverse effects on fetus, neonate
 - Congenital infections cross placenta, infect fetus *in utero*
 - Neonatal infections shortly before, during, after delivery

RISK FACTORS

- Maternal infection

COMPLICATIONS

- Premature birth; intrauterine growth restriction; tissue damage, related sequelae

SIGNS & SYMPTOMS

- Self-limiting to life-threatening conditions

DIAGNOSIS

- Maternal prenatal, delivery history; neonatal physical examination
- Imaging

LAB RESULTS

- Culture, serology testing

TREATMENT

- Address complications

MEDICATIONS

- Antimicrobials

VISIT...

LANZAROTE
Caliente.COM

CONGENITAL CYTOMEGALOVIRUS INFECTION

osms.it/congenital-CMV-infection

PATHOLOGY & CAUSES

- Clinical syndrome affects developing fetus, neonate
 - Caused by Cytomegalovirus (CMV) perinatal infection
 - Herpesvirus family
- Enveloped, double-stranded linear DNA, icosahedral viral capsid
 - Toxoplasmosis, other (syphilis, Varicella zoster, parvovirus B19), rubella, CMV, herpes (TORCH) infection
 - Tends to become latent, reactivate
- Highly-prevalent virus; not very contagious
 - Infects all ages
 - Approx. one-third of children are infected with CMV by age five
 - > half of adults are infected by age 40
- Virus spreads to fetus **transplacentally**/may be acquired via maternal genital contact during delivery/through breastmilk

Maternal infection

- Direct infectious body-fluid contact (e.g. **saliva**, **urine**, **sexually** transmitted); blood **transfusions**; **transplanted organs**; household contact, close contact with young infected children (e.g. daycare centers)
 - Usually **asymptomatic in adults**

RISK FACTORS

- Maternal infection

COMPLICATIONS

- Fetal/neonatal
 - Sensorineural **hearing loss** (SNHL), **chorioretinitis**, microcephaly, neurodevelopmental disability, seizure, anemia (hemolytic), pneumonitis, dental irregularity



Figure 131.1 Histological sections of chorionic villi demonstrating nuclear inclusions seen in congenital cytomegalovirus infection.

SIGNS & SYMPTOMS

- Birth
 - May be asymptomatic
- Small for gestational age, **petechial rash**, “**Blueberry muffin**” rash, hypotonia, weak suck, hepatosplenomegaly, jaundice

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan/MRI

- Neuroimaging
 - Intracranial calcification, ventriculomegaly, white matter disease, periventricular leukomalacia, corpus callosum dysgenesis, cerebellar hypoplasia

Auditory brainstem response (ABR)

- Hearing deficit

Ultrasound

- Suggestive prenatal fetal diagnostic findings
 - Growth restriction, **ventriculomegaly**, microcephaly, **periventricular calcification**, hepatic calcification, hydrops/ascites, echogenic bowel

LAB RESULTS

- Maternal prenatal, delivery history; positive maternal CMV immunoglobulin G (IgG), CMV immunoglobulin M (IgM) antibody; neonatal examination

Microbe identification

- Positive culture (urine, saliva)
- Polymerase chain reaction (PCR) (blood, urine, saliva)
- CMV antigens (pp65) in peripheral leukocytes

Blood studies

- ↑ liver transaminases
- ↑ direct, indirect serum bilirubin
- ↓ white blood cells (WBCs), ↓ platelets, ↓ red blood cells (RBCs)

TREATMENT

- Address complications

MEDICATIONS

- Antiviral therapy
 - Intravenous (IV) ganciclovir/oral (PO) valganciclovir

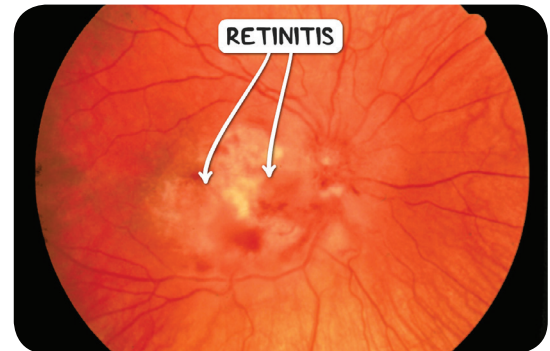


Figure 131.2 Retinal photograph demonstrating the necrotizing retinitis of CMV infection. The retinitis will typically spread in a “brush fire” pattern.

CONGENITAL RUBELLA SYNDROME

osms.it/congenital-rubella-syndrome

PATHOLOGY & CAUSES

- Syndrome caused by fetal rubella virus infection
 - Enveloped, positive-sense, single-stranded RNA virus
 - Rubivirus in *Togaviridae* family
 - Humans are only natural hosts

Maternal infection

- Occurs through droplet inhalation/direct infectious nasopharyngeal secretion contact → maternal viremia → hematogenous transplacental spread to fetus → persistent fetal infection

throughout gestation → virus-induced impaired cellular division, direct cytopathic effects

- Maternal–fetal transmission, congenital defect risk varies in accordance with maternal infection timing
 - ↑ ↑ **risk**: inoculation occurs during first ten gestational weeks
 - ↑ **risk**: cardiac, eye defects if inoculation occurs before eight gestational weeks
 - ↑ **risk**: hearing deficits if inoculation occurs up to 18 gestational weeks
 - ↓ **risk**: inoculation occurs after 18–20 gestational weeks

RISK FACTORS

- Maternal non-immunized status, infection

COMPLICATIONS

- Fetal growth restriction
- Hemolytic anemia, thrombocytopenia

Neurological, sensory defects

- Sensorineural hearing loss
- Cataracts, congenital glaucoma, pigmentary retinopathy, microphthalmia
- Microcephaly, meningoencephalitis, intellectual disability

Congenital heart defects

- Patent ductus arteriosus
- Pulmonary artery stenosis
- Coarctation of aorta

Vascular defects

- Intimal fibromuscular proliferation, arterial sclerosis, systemic hypertension (related to renal disease)
- May result in adult coronary, cerebral, peripheral vascular disease

Late complications

- Diabetes, thyroid disease, growth hormone deficiency, progressive rubella panencephalitis



Figure 131.3 Bilateral cataracts in a newborn baby as a consequence of congenital rubella infection.

SIGNS & SYMPTOMS

- “Blueberry muffin” rash
 - Purpuric rash indicates cutaneous hematopoiesis
- Small for gestational age; low birth weight
- Hepatosplenomegaly
- Jaundice
- Complications present (e.g. cataracts, heart defects)

DIAGNOSIS

DIAGNOSTIC IMAGING

MRI

- Head
 - Periventricular calcifications; demyelination
- Long bones
 - Radiolucent bone lesions; irregular, alternating longitudinal light, dark bands of density (“celery stalk” appearance)

LAB RESULTS

Viral identification

- Nasopharyngeal swabs, blood/cord blood, placenta, urine, cerebrospinal fluid (CSF)
 - PCR/culture: rubella-specific IgM (usually present at birth); persistent IgG

Prenatal diagnosis

- Viral isolation from amniotic fluid

OTHER DIAGNOSTICS

Maternal prenatal history

- Rubella exposure
- Neonatal exam

TREATMENT

- No specific treatment
- Address complications

Prevention

- Maternal MMR vaccination before conception

CONGENITAL SYPHILIS

osms.it/congenital-syphilis

PATHOLOGY & CAUSES

- Congenital infection caused by *Treponema pallidum* (spirochete bacterium causes syphilis)

Maternal infection

- Sexually
 - Direct infectious lesion contact → enters via microscopic abrasions → crosses placenta easily → fetal spirochetemia → widespread dissemination (almost all fetal organs) → congenital syphilis

RISK FACTORS

- Maternal infection → vertical (transplacental) → fetal transmission

COMPLICATIONS

- Stillbirth
- Premature birth
- Nonimmune **hydrops**
- Neurological
 - **Sensorineural hearing loss**, intellectual disability, seizures
- Hematologic
 - Hemolytic anemia, thrombocytopenia
- Renal
 - Nephrotic syndrome (immune complex mediated)
- Ophthalmologic
 - Chorioretinitis, uveitis, cataract, glaucoma, optic atrophy
- Gastrointestinal
 - Necrotizing enterocolitis, ileus, malabsorption
- Skeletal
 - Long-bone abnormalities, pathologic fractures

Treatment-related complications

- Benzathine penicillin G
 - **Jarisch–Herxheimer reaction**: release

of endotoxin-like compounds during penicillin-mediated lysis of *T. pallidum*
→ fever/chills, hypotension

SIGNS & SYMPTOMS

Early congenital syphilis

- General
 - Low birthweight, fever, hepatomegaly, jaundice, lymphadenopathy, pain-related ↓ extremity movement (pseudoparalysis)
- Mucocutaneous
 - Vesicular (pemphigus syphiliticus)/ maculopapular rash
 - Contagious, wart-like lesions (condylomata lata)
 - Syphilitic rhinitis (“snuffles”)
- Umbilical cord
 - Necrotizing funisitis (“barber-pole” appearance)

Late congenital syphilis

- Onset after two years old
- **Facial features**
 - Frontal bossing, **saddle nose**, **short maxilla**, protuberant mandible
- Sensory
 - Impaired vision/**hearing**
- Oropharynx
 - Hutchinson teeth (widely-spaced; **notched incisors**); mulberry molars (small, defective molars; cusps covered with globular enamel growths)
- Cutaneous
 - Gummas
- Skeletal
 - Anterior tibia bowing (**saber shins**), Higouménakis’ sign (sternoclavicular portion of clavicle enlargement), painless arthritis (Clutton’s joints), scaphoid scapula



Figure 131.4 A newborn baby with a saddle nose malformation and snuffles, both of which are signs of congenital syphilis infection.

DIAGNOSIS

DIAGNOSTIC IMAGING

Long-bone radiographs

- Multiple anomalies
 - E.g. metaphyseal lucent bands, metaphyseal “sawtooth” serration (Wegener sign), “moth-eaten” appearance

Chest X-ray

- Diffuse infiltrate/opacification of both lung fields (“pneumonia alba”)

LAB RESULTS

- *T. pallidum* identification
 - Dark field microscopy
 - Direct fluorescent antibody (DFA) staining (nasal secretions, placenta, umbilical cord, autopsy tissue)
 - Reactive venereal disease research laboratory (VDRL), rapid plasma reagin (RPR)
- Blood studies
 - ↓ platelets, ↑ ↓ WBCs
- CSF analysis
 - Reactive VDRL, pleocytosis, ↑ protein, *T. pallidum* DNA presence (identified by PCR)

TREATMENT

MEDICATIONS

- Intramuscular (IM) benzathine penicillin G

Prevention

- Screening at first prenatal visit
 - IM benzathine penicillin G

OTHER INTERVENTIONS

Prevention

- Characteristic fetal congenital infection features detectable via ultrasound
 - 18–22 weeks of gestation

GROUP B STREPTOCOCCUS (GBS) INFECTION

osms.it/group-b-strep-infection

PATHOLOGY & CAUSES

- Serious neonatal infection caused by *Streptococcus agalactiae*
 - **Gram-positive**, encapsulated diplococcus
 - Commonly colonizes maternal gastrointestinal, **genital tracts**
 - Produces complete (beta hemolysis) on blood agar plates
- Acquired via intra-amniotic infection, ascending infection after amniotic membrane rupture/during birth canal passage

Classification

- GBS onset timing
 - **Early-onset GBS**: presents between 24 hours to six days post-delivery (most common)
 - **Late-onset GBS**: 4–5 weeks post-delivery
 - **Late, late-onset GBS**: presents in infants > three months (most common in infants with immunodeficiency history/born < 28 gestational weeks)

RISK FACTORS

- GBS-positive intrapartum nucleic acid amplification test (NAAT)
- Chorioamnionitis
- Preterm labor
- Premature membrane rupture ≥ 18 hours

Maternal presentation

- Delivery time
 - Intrapartum fever ≥ 38°C/100.4°F
 - Delivery < 37+0 gestational weeks
 - GBS bacteriuria in current pregnancy

Demographic risk factors

- Young maternal age

- Biologically-female individuals of African descent

COMPLICATIONS

- Bacteremia
- **Sepsis**; septic shock
- Pulmonary hypertension (PPHN)
- Focal infections
 - **Meningitis**, **pneumonia**, endocarditis, septic arthritis, osteomyelitis, cellulitis, adenitis
- ↑ preterm infant mortality

SIGNS & SYMPTOMS

- Lethargy/irritability; poor feeding
- Temperature instability
- Respiratory symptoms
 - E.g. tachypnea, grunting, retractions, apnea, hypoxemia/↓ oxygen saturation
- Hypotension
- Bulging fontanel, nuchal rigidity (GBS meningitis)
- ↓ extremity movement/pain with manipulation GBS bone/joint infection

DIAGNOSIS

DIAGNOSTIC IMAGING

Chest X-ray

- Diffuse alveolar infiltrates, pleural effusion indicate GBS pneumonia

LAB RESULTS

Neonatal blood studies

- ↑ ↓ absolute neutrophil count
- ↓ platelet count
- **Positive blood culture**

- ↑ C-reactive protein (CRP)

Neonatal CSF analysis

- ↑ protein level, WBC count
- ↓ glucose level
- Positive Gram stain, culture results

Urinalysis

- Gram stain, culture
 - Presence of nitrates, leukocyte esterase, bacteria

TREATMENT

MEDICATIONS

- Antibiotics
 - Penicillin G, ampicillin, nafcillin

Prevention

- Vaginal-rectal culture: 35–37 gestational weeks
 - If positive culture → intrapartum antibiotic prophylaxis
 - Penicillin, ampicillin, cefazolin

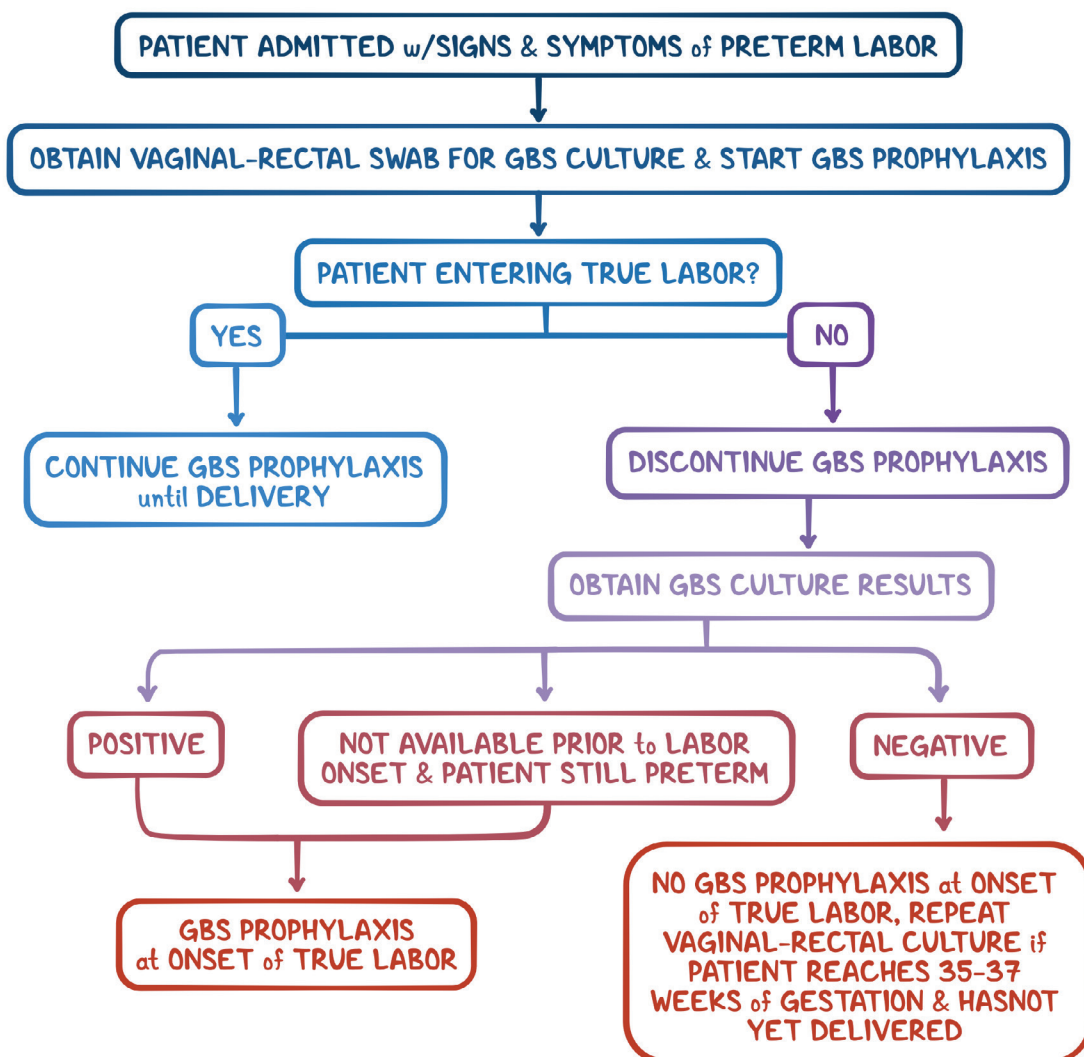


Figure 131.5 Algorithm for GBS screening and prophylaxis.

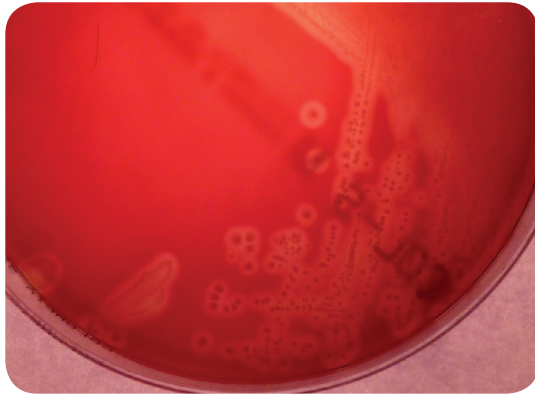


Figure 131.6 Group B streptococcus colonies cultured on blood agar.

NEONATAL CONJUNCTIVITIS

osms.it/neonatal-conjunctivitis

PATHOLOGY & CAUSES

- Clinical infection manifestation occurs within first four weeks of life, AKA ophthalmia neonatorum
 - Most commonly caused by *Neisseria gonorrhoeae*/*Chlamydia trachomatis* (coinfection with both microbes common)
 - Rarely, herpetic conjunctivitis caused by herpes simplex virus (HSV)
 - *Staphylococcus*, *Streptococcus* may also be implicated in some conjunctival infections

Transmission

- Primarily via exposure to mother's infected genital flora during vaginal birth
- Ascending infection in case of premature membrane rupture

RISK FACTORS

- Maternal infection

COMPLICATIONS

- Corneal ulceration, scarring
- Vision impairment, blindness
- Systemic sequelae of infection
- HSV: keratitis, keratouveitis

SIGNS & SYMPTOMS

- Eyelid swelling, watery/mucopurulent discharge, chemosis, micropannus (granulation tissue membrane)



Figure 131.7 The clinical appearance of severe neonatal conjunctivitis.

DIAGNOSIS

LAB RESULTS

Microbe identification

- Conjunctival, nasopharyngeal specimens
 - Culture
 - Gram stain
 - Nucleic acid amplification test (NAAT)
 - Polymerase chain reaction (PCR)
 - Direct fluorescent antibody (DFA), enzyme immunoassay (EIA) tests
 - HSV: Giemsa stain, PCR

CBC

- ↑ eosinophil count

OTHER DIAGNOSTICS

- Maternal history
- No prenatal care; untreated *C. trachomatis*/*N. gonorrhoeae* infection; neonatal examination

TREATMENT

- Antibiotics
 - *Gonococcal disease*: IV/IM ceftriaxone
 - *Chlamydial disease*: oral erythromycin, azithromycin
 - *HSV*: acyclovir

Prevention

- Gonococcal conjunctivitis
 - Routine neonatal prophylaxis with erythromycin 0.5% ointment

OTHER INTERVENTIONS

- Treat neonate's mother, sexual partner
- Maternal prenatal screening

NEONATAL HERPES SIMPLEX

osms.it/neonatal-herpes-simplex

PATHOLOGY & CAUSES

- Uncommon, serious neonatal infection caused by herpes simplex virus (HSV-1, HSV-2)
- Enveloped, double-stranded DNA virus
 - HSV-2: most neonatal cases
 - TORCH infection

Transmission

- Intrauterine/transplacentally is rare
- *Intrapartum*: ascending infection from maternal genitals during delivery/mother's infected genital flora exposure
 - Most maternal HSV infections are clinically inapparent
- Postnatal via close contact

Inoculation

- 2–21 day incubation
- Skin, eyes, mouth (SEM) disease
- Central nervous system (CNS) disease
- Disseminated disease
 - Multiple organs (e.g. lungs, liver, adrenal, CNS, skin, eye, mouth)

RISK FACTORS

Maternal infection

- ↑ transmission risk with vaginal delivery, prolonged membrane rupture, delivery instruments that disrupt fetal skin barrier

COMPLICATIONS

- Recurring skin lesions throughout childhood

- CNS HSV
 - Meningoencephalitis
- Disseminated HSV
 - Hepatitis, disseminated intravascular coagulation (DIC), hemorrhagic pneumonitis
 - High mortality

SIGNS & SYMPTOMS

- May be asymptomatic initially
- SEM
 - Mucosal vesiculopustular eruption
- CNS HSV
 - Temperature instability, irritability/lethargy, bulging fontanelle, seizure
- Disseminated HSV
 - Temperature instability, lethargy, poor feeding, jaundice, hepatosplenomegaly, respiratory distress



Figure 131.8 A neonate with herpes simplex vesicles on the scalp.

DIAGNOSIS

LAB RESULTS

- Microbe identification
 - Culture (blood, CSF, urine, mucous membrane fluid)
 - PCR
- CNS analysis
 - CSF ↑ protein, ↑ mononuclear pleocytosis
- Lesion analysis
 - Multinucleated giant cells visualized with Giemsa/Wright stain

TREATMENT

MEDICATIONS

- IV acyclovir

OTHER INTERVENTIONS

- Also treat mother, mother's partner

NEONATAL MENINGITIS

osms.it/neonatal-meningitis

PATHOLOGY & CAUSES

- Severe neurological infection complication
 - High morbidity, mortality rate
 - Most often occurs during first week of life
 - Bacterial, viral, fungal infections
- Usually caused by **variety of bacteria** (e.g. GBS, *E. coli*, *S. pneumoniae*, *Enterococcus*, coagulase-negative staphylococci, *S. aureus*, *L. monocytogenes*, *H. influenzae*)

RISK FACTORS

- Premature birth, low birthweight, maternal infection, sepsis

COMPLICATIONS

- Cerebral edema/abscess, hydrocephalus, intraventricular hemorrhage, encephalomalacia, cerebral palsy, seizure disorder, auditory/visual sensory deficits

SIGNS & SYMPTOMS

General

- Temperature instability, lethargy, poor feeding, vomiting, diarrhea

Neurological

- Irritability, hypotonia, tremors, seizures, full/bulging fontanelle; may have nuchal rigidity

Respiratory

- Tachypnea, retractions nasal flaring, grunting, apnea

DIAGNOSIS

DIAGNOSTIC IMAGING

Cranial sonography

- Assess ventricular size
 - Detect ventricular hemorrhage,

ventriculitis, extracerebral fluid collections

MRI/CT scan

- Detects cerebral edema, infarction/abscess area, CSF obstruction, encephalomalacia, atrophic tissue (cortical, white matter)

LAB RESULTS

- Microbe identification
 - CSF
 - Gram stain, culture, PCR, NAAT
 - Blood culture (may be negative)
 - Urine culture
- Blood studies
 - ↑↓ WBC count, left shift, ↓ platelets
- CSF
 - ↑ WBCs, ↑ protein, ↓ glucose

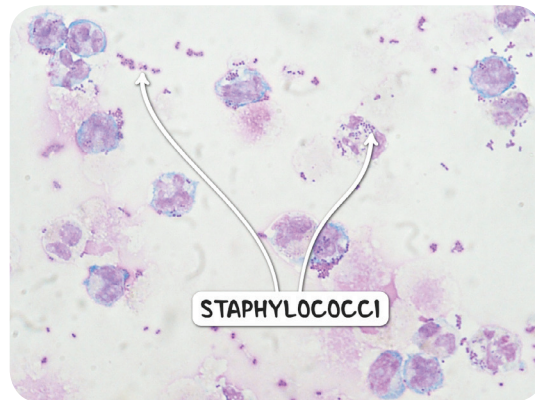


Figure 131.9 A sample of cerebrospinal fluid from a neonate with meningitis. There are neutrophils present, denoting an acute inflammatory process as well as cocci arranged in groups and pairs. Culture grew *Staphylococcus capitis*.

TREATMENT

MEDICATIONS

- Antimicrobials
 - usually ampicillin + gentamicin + third-generation cephalosporin
- Anticonvulsants
- IV fluids, vasopressors

NEONATAL SEPSIS

osms.it/neonatal-sepsis

PATHOLOGY & CAUSES

- Serious infection; presents within neonate's first 30 days; characterized by bacteremia/meningitis
- Characterized by onset
 - **Early-onset sepsis**: occurs with first 3–7 days
 - **Late-onset sepsis**: occurs between 7–30 days
- May be bacterial (most common), viral, fungal (more common in preterm infants)
→ vertical transmission before/during labor/delivery

RISK FACTORS

- Low birthweight
- Preterm birth
- Low Apgar score at five minutes
- Prolonged membrane rupture
- Chorioamnionitis
- Maternal GBS colonization (inadequate intrapartum treatment)
- Inborn metabolism errors
- Maternal age ≤ 20

COMPLICATIONS

- Meningitis, pneumonia, multi-organ failure, necrotizing enterocolitis (NEC), high mortality rate

SIGNS & SYMPTOMS

- May be initially nonspecific
- Fever, temperature instability

General signs

- Lethargy, irritability, poor suck, hypotonia

Respiratory distress signs

- Tachypnea, grunting, nasal flaring, retractions, apneic periods, cyanosis

Hemodynamic instability

- Tachycardia/bradycardia, prolonged capillary refill time, hypotension, pallor

DIAGNOSIS

- Maternal, intrapartum, neonatal history
- Compatible clinical presentation

LAB RESULTS

- Blood, CSF culture
 - Identify causative microbe
- CBC
 - Neutropenia (due to small neutrophil storage pool)
- CSF analysis
 - $\uparrow$ WBCs; protein, glucose may also be $\uparrow$

TREATMENT

MEDICATIONS

- Antibiotics
- Vasopressors

OTHER INTERVENTIONS

- Supplemental oxygen, mechanical ventilation
- IV fluids

TOXOPLASMOSIS

osms.it/toxoplasmosis

PATHOLOGY & CAUSES

- Congenital infection
 - Caused by protozoa *Toxoplasma gondii*
 - TORCH infection
- Obligate intracellular parasite
- Transplacental transmission to fetus

Biphasic life cycle

- Sexual cycle
 - Occurs exclusively in felines (definitive host)
- Asexual cycle
 - Occurs in other animals, including humans

Maternal infection routes

- Cats consume infective form (cysts) from prey (e.g. intermediate hosts—rodents, birds) → replication within intestines → oocyst formation → fecal excretion → maternal infection via cat fecal exposure (soil, litter box)
- Wild game/animals bred for human consumption (e.g. cattle) may ingest environmental oocytes → infection → maternal consumption of raw/undercooked meat, contaminated water/vegetables → maternal infection

RISK FACTORS

- Maternal infection
 - Primary infection during pregnancy/ reactivation in immunocompromised host

COMPLICATIONS

- ↑ congenital effect severity when infection occurs early in gestation
 - **Classic triad:** chorioretinitis, hydrocephalus, intracranial calcification
 - Sensorineural hearing loss, microcephaly, intellectual disability, motor/cerebellar dysfunction, growth delay, seizure, pneumonitis, anemia, thrombocytopenia

SIGNS & SYMPTOMS

Subclinical infection

- Routine assessment reveals no anomalies
- Focused examination may reveal infection signs (e.g. ophthalmologic, CNS imaging)

Clinically apparent disease

- During neonatal period/first few months of life
 - May be mild/severe, CNS/ocular complications, purpuric rash ("blueberry muffin" rash), fever, jaundice, hepatosplenomegaly, lymphadenopathy, microphthalmia, hypotonia

Late infancy, childhood, adolescence

- Undiagnosed/untreated infection emergence/relapse
 - Complication developments (e.g. chorioretinitis, neurosensory hearing loss)
 - Growth delay, endocrine abnormalities secondary to hypothalamic, pituitary dysfunction

DIAGNOSIS

DIAGNOSTIC IMAGING

ABR

- Sensorineural hearing loss

CT scan

- Neuroimaging
 - Intracranial calcifications, hydrocephalus (ventriculomegaly), cortical atrophy

LAB RESULTS

Confirmatory diagnostics

- With any of following
 - Positive IgG with positive IgM (after five days of life), IgA (after ten days of life) + confirmed maternal serology
 - Positive CSF PCR + confirmed maternal *T. gondii* infection during pregnancy, characteristic neonatal clinical findings
 - Positive IgG beyond 12 months of age demonstrates anti-*Toxoplasma* IgG persistence

Ophthalmic examination

- Chorioretinitis

Neurologic examination

- Lumbar puncture
 - ↑ protein, mononuclear pleocytosis

Blood studies

- CBC
 - ↓ RBCs ↓ platelets, ↑ eosinophils
- Liver function tests
 - Possible ↑ aspartate aminotransferase; alanine aminotransferase; total, direct bilirubin

Cytologic placental examination

- *T. gondii* cyst/tachyzoite presence

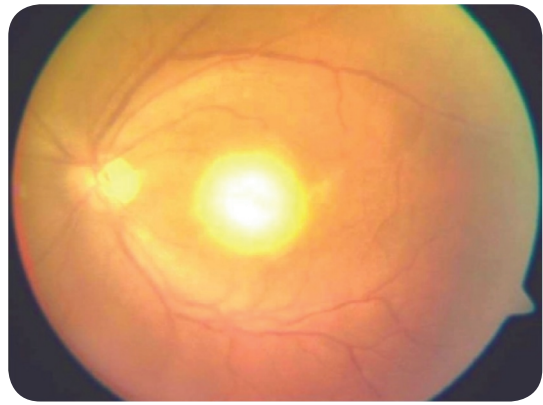


Figure 131.10 Retinal photograph demonstrating the characteristic “headlight in the fog” appearance of toxoplasma retinitis.

TREATMENT

MEDICATIONS

Neonatal treatment

- Antiparasitic therapy
 - Pyrimethamine + sulfadiazine + folinic acid
- Prednisone if ↑ CSF protein

Prevention

- Maternal antiparasitic therapy
 - Positive amniotic fluid PCR before 18 gestational weeks
- Pyrimethamine + sulfadiazine plus folinic acid until delivery